REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 1-2, 5-25, 27-40, and 102-165, the only claims pending and under examination in this application.

Claims 1, 102, 104, 122, 124, 148, 151, 157, and 160 have been amended to clarify the claim language. No new matter has been added. As no new matter has been added by way of this amendment, entry thereof by the Examiner is respectfully requested.

Independent Claims 1, 102, 122, 148, and 157 have been amended to clarify that the method recited in the claims is a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, Claims 1, 102, 122, 148, and 157 have been amended to clarify that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control. Support for the amendments can be found in throughout the specification and claims as originally filed at, for example, page 11, lines 12-25; page 29, line 16 to page 30, line 8; page 56, lines 8-30; and page 60, lines 25-33.

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 1-2, 5-25, 27-40, 104, 124, 151, and 160 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As indicated above, Claims 1, 102, 104, 122, 124, 148, 151, 157, and 160 have been amended to clarify the claim language. In view of these amendments, the Applicants respectfully submit that the meaning of the claims is clear. Therefore, the Applicants respectfully request that the 35 U.S.C. § 112 rejection of Claims 1-2, 5-25, 27-40, 104, 124, 151, and 160 be withdrawn.

Claim Rejections – 35 U.S.C. § 103

Claims 1-2, 10-12, 15-22, 37, 39, 40, 102-104, 106-112, 119-124, 126-132, 139-151, and 153-156 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Southern et al. (*Nucleic Acids Research*, 1994, vol. 22, pp. 1368-73) (hereinafter "Southern (1994)"), in view of Southern (*Current Opinions in Biotechnology*, 1996, vol. 7, pp. 85-88) (hereinafter "Southern (1996)"), in view of Drmanac et al. (*Genomics*, 1989, vol. 4, pp. 114-28).

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103 the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations. See *Pharmastem Therapeutics v. Viacell et al.*, 2007 U.S. App. LEXIS 16245 (Fed. Cir. 2007) ("the burden falls on the patent challenger to show by clear and convincing evidence that a person of ordinary skill in the art would have had reason to attempt to make [every element of] the composition or device, or carry out the [entire] claimed process, and would have had a reasonable expectation of success in doing so," (citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007))); and see *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) ("[t]he Supreme Court recently explained that 'a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art,'" (citing *KSR Int'l Co.* at 1741)); and see *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006) ("[once] all claim limitations are found in a number of prior art references, the factfinder must determine '[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references,'" (citing *In re Fulton*, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004))).

Independent Claims 1, 102, 122, 146, 148, and 157 are directed to a computer system and computer based methods for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. As indicated above, independent Claims 1, 102, 122, 148, and 157 have been amended to clarify that the

method recited in the claims is a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence and that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

The Examiner alleges that Southern (1994) substantially discloses the claimed invention, but is deficient in that Southern (1994) fails to teach the step of predicting the hybridization of the oligonucleotide by the presence of said hybridization cluster, and fails to teach sequential overlapping oligomers of equal length. Thus, to remedy these deficiencies, the Examiner relies upon Southern (1996) and Drmanac, respectively.

Specifically, the Examiner alleges that Figures 3 and 4 of Southern (1994) illustrate a "rung darkness" parameter that represents hybridization intensity. See Southern (1994), Figures 3 and 4. The Examiner further alleges that, based on this "rung darkness" parameter, several clusters of darker colors are selected and identified through arrows with numbers, which represent the length of the oligonucleotides. See Southern (1994), Figure 3c. Thus, the Examiner concludes that Southern (1994) discloses qualitative rankings between clusters based on both cluster size and lengths of oligonucleotides within the clusters. However, the Examiner acknowledges that Southern (1994) does not teach predicting the hybridization of the oligonucleotide by the presence of said hybridization cluster or sequential overlapping oligomers of equal length.

In addition, the Examiner equates the Southern (1996) disclosure of a "[c]omparison of the hybridization patterns of wild-type and mutant sequences to an array of oligonucleotides complementary to the wild-type" with the claimed element of "selecting, for a cluster, a hybridization oligonucleotide wherein the hybridization of said hybridization oligonucleotide is predicted by the presence of said hybridization oligonucleotide in said cluster".

The Applicants respectfully disagree and contend that a *prima facie* case of obviousness has not been established because the cited combination fails to teach every element of the rejected claims. Southern (1994) is directed to a method for making arrays of oligonucleotides corresponding to a full set of complements of a known sequence in a single series of base couplings in which each base in the complement is added in turn. See Southern (1994), pg. 1368, Abstract, first sentence. Southern (1994) indicates that the disclosed array method provides an empirical method for analyzing the interactions of a target molecule with a complete set of complementary oligonucleotides. See Southern (1994), pg. 1373, Discussion, last sentence. Consequently, Southern (1994) does not disclose or suggest a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, Southern (1994) does not disclose or suggest that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

Southern (1996) presents a review of high-density gridding techniques and applications. See Southern (1996), pg. 85, Introduction. Southern (1996) discusses applications for oligonucleotide arrays and hypothesizes that dedicated arrays will be useful for mutation detection by comparing the hybridization patterns of wild-type and mutant sequences to an array of oligonucleotides complementary to the wild-type. See Southern (1996), pg. 86-87. Thus, similar to Southern (1994), Southern (1996) only teaches or suggests empirical methods of observing oligonucleotide hybridization. Southern (1996) merely proposes possible hybridization experiments that may be performed using oligonucleotide arrays and suggests that differences will be observed when comparing the hybridization patterns of wild-type and mutant sequences. As such, Southern (1996) does not disclose or suggest a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, Southern (1996) does not disclose or suggest that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

Drmanac was cited solely for the disclosure of sequential overlapping oligomers of equal length. See Drmanac, pg. 115, FIG.1. As such, Drmanac fails to remedy the deficiencies in Southern (1994) and Southern (1996) discussed above. Specifically, Drmanac discusses performing probability calculations to determine the numbers of oligonucleotide probes, lengths and types of cloned fragments, numbers of clones, and numbers of hybridizations necessary for sequencing by hybridization. See Drmanac, page 115, col. 1, paragraph 3; page 122, col. 2, Appendix A1. As such, Drmanac does not disclose or suggest a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, Drmanac does not disclose or suggest that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

Therefore, the Applicants contend that a *prima facie* case of obviousness has not been established because the recited combination fails to teach or suggest all the elements of the rejected claims. Consequently, the Applicants contend that the cited combination of references does not render Claims 1-2, 10-12, 15-22, 37, 39, 40, 102-104, 106-112, 119-124, 126-132, 139-151, and 153-156 obvious and respectfully request that the 35 U.S.C. § 103(a) rejection be withdrawn.

Claim 13 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Southern (1994), in view of Southern (1996), in view of Drmanac, and further in view of Southern et al. (*Genomics*, 1992, vol. 13, pp. 1008-17) (hereinafter "Southern (1992)").

Claim 13 ultimately depends from Claim 1. Claim 1 is directed to a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. As set forth above, Claim 1 has been amended to clarify that the method recited in the claims is a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence and that

the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

The Examiner alleges that the combination of Southern (1994), Southern (1996), and Drmanac substantially disclose the claimed invention, but are deficient in that they do not teach the method of statistical sampling with dimensionless numbers. Thus, to remedy this deficiency, the Examiner relies upon Southern (1992).

The Applicants respectfully disagree and contend that a *prima facie* case of obviousness has not been established because the cited combination fails to teach every element of the rejected claims. As discussed above, Southern (1994) indicates that the disclosed array method provides an *empirical method* for analyzing the interactions of a target molecule with a complete set of complementary oligonucleotides. See Southern (1994), pg. 1373, Discussion, last sentence. Similar to Southern (1994), Southern (1996) only teaches or suggests empirical methods of observing oligonucleotide hybridization. See Southern (1996), pg. 86-87. Consequently, neither Southern (1994) nor Southern (1996) discloses or suggests a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, neither Southern (1994) nor Southern (1996) discloses or suggests that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

As set forth above, Drmanac discusses performing probability calculations to determine the numbers of oligonucleotide probes, lengths and types of cloned fragments, numbers of clones, and numbers of hybridizations necessary for sequencing by hybridization. See Drmanac, page 115, col. 1, paragraph 3; page 122, col. 2, Appendix A1. As such, Drmanac does not disclose or suggest a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, Drmanac does not disclose or suggest that

the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

Southern (1992) was cited solely for the disclosure of ranks and dimensionless scores of sequences. See Southern (1992), pg. 1013, TABLES I and II. As such, Southern (1992) fails to remedy the deficiencies in Southern (1994), Southern (1996), and Drmanac discussed above.

Therefore, for the reasons stated above, a *prima facie* case of obviousness has not been established because the cited combination of references fails to teach or suggest every element of the rejected claims. Accordingly, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claim 13 be withdrawn.

Claims 5-7, 23-24, 30-36, 105, 113-118, 125, 133-138, 152, and 157-165 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Southern (1994), in view of Southern (1996), in view of Drmanac, and further in view of Petersheim et al. (*Biochemistry*, 1983, vol. 22, pp. 256-263).

Independent Claims 1, 102, 122, 148, and 157 are directed to computer based methods for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. As indicated above, independent Claims 1, 102, 122, 148, and 157 have been amended to clarify that the method recited in the claims is a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence and that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

The Examiner alleges that the combination of Southern (1994), Southern (1996), and Drmanac substantially discloses the claimed invention, but is deficient in that it fails to disclose the elements of specific thermodynamic parameters for calculations, specific computational requirements, and thermodynamic cut-off values,

as claimed by the Applicants. Thus, the Examiner relies upon Petersheim to remedy these deficiencies.

The Applicants respectfully disagree and contend that a *prima facie* case of obviousness has not been established because the cited combination fails to teach every element of the rejected claims. As discussed above, Southern (1994) indicates that the disclosed array method provides an empirical method for analyzing the interactions of a target molecule with a complete set of complementary oligonucleotides. See Southern (1994), pg. 1373, Discussion, last sentence. Similar to Southern (1994), Southern (1996) only teaches or suggests empirical methods of observing oligonucleotide hybridization. See Southern (1996), pg. 86-87. As such, neither Southern (1994) nor Southern (1996) discloses or suggests a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, neither Southern (1994) nor Southern (1996) discloses or suggests that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

As set forth above, Drmanac discusses performing probability calculations to determine the numbers of oligonucleotide probes, lengths and types of cloned fragments, numbers of clones, and numbers of hybridizations necessary for sequencing by hybridization. See Drmanac, page 115, col. 1, paragraph 3; page 122, col. 2, Appendix A1. As such, Drmanac does not disclose or suggest a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, Drmanac does not disclose or suggest that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

Petersheim was cited solely for the disclosure of using thermodynamics to analyze the structure and stability of double helices. See Petersheim, pg. 256,

Abstract. As such, Petersheim fails to remedy the deficiencies in Southern (1994), Southern (1996), and Drmanac discussed above.

Therefore, for the reasons stated above, a *prima facie* case of obviousness has not been established because the cited combination of references fails to teach or suggest every element of the rejected claims. Accordingly, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 5-7, 23-24, 30-36, 105, 113-118, 125, 133-138, 152, and 157-165 be withdrawn.

Claims 8-9 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Southern (1994), in view of Southern (1996), in view of Drmanac, and further in view of McMahon et al. (U.S. Patent No. 5,310,650).

Claims 8-9 depend from Claim 1. Claim 1 is directed to a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. As indicated above, Claim 1 has been amended to clarify that the method recited in the claims is a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence and that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

The Examiner alleges that the cited combination of Southern (1994), Southern (1996), and Drmanac substantially disclose the claimed invention, but is deficient in that it fails to teach the kinetic properties and coupling efficiencies of the reactions. Thus, to remedy this deficiency, the Examiner relies upon McMahon.

The Applicants respectfully disagree and contend that a *prima facie* case of obviousness has not been established because the cited combination fails to teach every element of the rejected claims. As discussed above, Southern (1994) indicates that the disclosed array method provides an empirical method for analyzing the interactions of a target molecule with a complete set of complementary

oligonucleotides. See Southern (1994), pg. 1373, Discussion, last sentence. Similar to Southern (1994), Southern (1996) only teaches or suggests empirical methods of observing oligonucleotide hybridization. See Southern (1996), pg. 86-87. As such, neither Southern (1994) nor Southern (1996) discloses or suggests a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, neither Southern (1994) nor Southern (1996) discloses or suggests that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

As set forth above, Drmanac discusses performing probability calculations to determine the numbers of oligonucleotide probes, lengths and types of cloned fragments, numbers of clones, and numbers of hybridizations necessary for sequencing by hybridization. See Drmanac, page 115, col. 1, paragraph 3; page 122, col. 2, Appendix A1. As such, Drmanac does not disclose or suggest a computer based method for selecting a hybridization oligonucleotide to hybridize to a target nucleotide sequence. In addition, Drmanac does not disclose or suggest that the determining and evaluating of parameters that are predictive of the ability of the oligonucleotides to hybridize to the target nucleotide sequence are performed using an algorithm under computer control.

McMahon was cited solely for the disclosure of kinetics and coupling efficiencies of hybridizations. See McMahon, col. 13, lines 25-37 and TABLE I. As such, McMahon fails to remedy the deficiencies in Southern (1994), Southern (1996), and Drmanac discussed above.

Therefore, for the reasons stated above, a *prima facie* case of obviousness has not been established because the cited combination of references fails to teach or suggest every element of the rejected claims. Accordingly, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 8-9 be withdrawn.

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone John Brady at (408) 553-3584.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10971464-3.

Respectfully submitted,

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